MIRTAZAPINE 15MG ORODISPERSIBLE TABLETS
PL 08608/0114
PL 08608/0117

MIRTAZAPINE 30MG ORODISPERSIBLE TABLETS
PL 08608/0115
PL 08608/0118

MIRTAZAPINE 45MG ORODISPERSIBLE TABLETS
PL 08608/0116
PL 08608/0119

UKPAR

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MIRTAZAPINE 45MG ORODISPERSIBLE TABLETS
PL 08608/0116
PL 08608/0119

LAY SUMMARY

The MHRA granted Olinka UK Limited Marketing Authorisations (licences) for the medicinal products Mirtazapine 15mg Orodispersible Tablets (PL 08608/0114 and PL 08608/0117); Mirtazapine 30mg Orodispersible Tablets (PL 08608/0115 and PL 08608/0118) and Mirtazapine 45mg Orodispersible Tablets (PL 08608/0116 and PL 08608/0119) on 24th July 2007. These are prescription-only medicines (POM) used for the treatment of depression.

These products contain the active substance mirtazapine.

The test products were considered essentially similar to the previously granted applications Zispin® Soltab 15mg, 30mg and 45mg Orodispersible Tablets (Organon Laboratories Ltd). No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Mirtazapine 15mg, 30mg and 45mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

MIRTAZAPINE 15MG ORODISPERSIBLE TABLETS
PL 08608/0114
PL 08608/0117

MIRTAZAPINE 30MG ORODISPERSIBLE TABLETS
PL 08608/0115
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MIRTAZAPINE 45MG ORODISPERSIBLE TABLETS
PL 08608/0116
PL 08608/0119

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Mirtazapine 15mg, 30mg and 45mg Orodispersible Tablets (PL 08608/0114-0119) on 24th July 2007. The products are prescription-only medicines.

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claming essential similarity to the previously approved applications Zispin® Soltab 15mg, 30mg and 45mg Orodispersible Tablets granted to Organon Laboratories Ltd on the 15th July 2003. In turn these applications had demonstrated equivalence to the approved product, Remeron 15mg, 30mg and 45mg tablets (N.V. Organon, Netherlands). The originator products have been authorised in the EU since March 1994 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient mirtazapine and are indicated for the treatment of depressive illness.

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

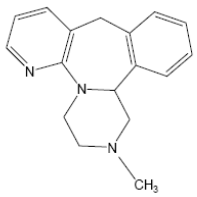
These applications for Mirtazapine 15mg, 30mg and 45mg Orodispersible Tablets were submitted at the same time and depend on the bioequivalence studies comparing the applicant's 30mg tablets against Zispin® SolTab of the same strength. Consequently, sections of this Scientific Discussion refer to all products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Mirtazapine

INN:	Mirtazapine
Chemical Names:	(RS)-1,2,3,4,10,14b-Hexahydro-2-methylpyrazino-[2,1-α]pyrido[2,3-c][2]benzazepine 2-methyl-1,2,3,4,10,14b-hexahydro benzo [c]pyrozino[1,2- α]pyrido[3,2-f]-azepine 6-Azamianserin
CAS No:	61337-67-5



Molecular formula:	$C_{17}H_{19}N_3$
Molecular weight:	265.36g/mol
Physical form:	White to yellowish white crystals or crystalline powder.
Solubility:	Freely soluble in methanol, N,N-dimethyl formamide and ethanol, and practically insoluble in water. Slightly soluble in buffer solutions at pH 2 and pH 4, insoluble at pH 9.
Melting range:	112^{o}C -118^{o}C

The drug substance specification provided is acceptable.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active mirtazapine is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated that support the retest period for the drug substance when stored in the proposed packaging.

Certificates of analysis for the reference standards and impurities have been provided.

DRUG PRODUCT
Other ingredients

Ingredient	Reference to standard
Active ingredient	
Mirtazapine	HSE
Excipient	
Mannitol DC	Ph.Eur
Microcrystalline Cellulose Avicel Ph-102	Ph.Eur
Low-substituted Hydroxypropyl Cellulose	USP
Crospovidone	Ph.Eur
Silica, Colloidal Anhydrous	Ph.Eur
Purified Water	Ph.Eur
Microcrystalline Cellulose and Guar Gum	HSE
Aspartame E951	Ph.Eur
Magnesium Stearate	Ph.Eur
Orange Flavour 1209603133 Silesia	HSE
Magnesium Carbonate Heavy	Ph.Eur
L-Methionine	Ph.Eur

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all the excipients. None of the excipients are novel or contain material of animal or human origin. There are no overages.

Dissolution profile
Dissolution profiles for all three strengths of the drug product were found to be similar to those for the reference products.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Product is packaged in either blisters composed of aluminium and polyvinyl chloride (PVC) or containers composed of either polypropylene (PP) or high density polyethylene (HDPE). Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 tablets.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are "Do not store above 25 degrees".

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

General

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. It is related to tricyclic antidepressants. It is a presynaptic alpha-antagonistic, increases central noradrenergic and serotonergic neurotransmission. It is claimed to have few antimascurinic effects, but causes sedation during initial treatment. It is said to be more effective in the presence of symptoms such as psychomotor inhibition, sleep disturbances (early wakening) and weight loss.

Pharmacodynamics

Mirtazapine is a centrally active presynaptic alpha2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-hydroxytryptamine (5-HT) receptors.

The histamine H1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

Pharmacokinetics

Following oral administration, mirtazapine is rapidly absorbed, reaching peak plasma levels after about two hours. It has a bioavailability of approximately 50%. Binding of mirtazapine to plasma proteins is about 85%. The mean elimination half-life is 20-40 hours. Steady state is reached following 3-4 days of dosing; after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine.

Mirtazapine is extensively metabolised and eliminated via urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. The clearance mirtazapine may be decreased as a result of renal or hepatic insufficiency.

Bioequivalence

The applicant has submitted a comparative, randomised, single-dose, 3-way Crossover bioavailability study of Pharmaco 30 mg orodispersible mirtazapine tablets, Organon Laboratories Limited (Zispin®) 30 mg mirtazapine tablets and Organon Laboratories Limited (Remergil® Soltab^{TM}) 30 mg orodispersible mirtazapine tablets in 42 healthy adult males under fasting conditions. In each period, subjects were housed from at least 12 hours before dosing until after the 36-hour post-dose events and returned for the 48-, 72-, and 96-hour post-dose events. Single oral 30 mg doses were separated by a washout period of 21 days between each period.

The AUC_{0-t}, AUC_{inf}, AUC/AUC_{inf}, C_{max}, t_{max}, half-life, and kel; pharmacokinetic (PK) parameters were calculated for plasma mirtazapine. The analysis of variance (ANOVA) model included sequence, formulation and period as fixed effects and subjects nested within sequence as a random effect. The 90% confidence intervals for

the ratios were derived by exponentiation of the confidence intervals obtained for the difference between formulation least-squares means (LSM) resulting from the analyses on the In-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf}, and C_{max}.

A summary of the main pharmacokinetic parameters for mirtazapine are presented in tables 1 & 2 below.

Table 1
Project No: AA19376
Summary of Results – Mirtazapine in Plasma
Pharmacokinetic Parameters
(N = 42)

	ln AUC_{0-t}* (ng•h/ml)	ln AUC_{inf}* (ng•h/ml)	ln C_{max}* (ng/ml)	t_{max} (h)	Half-life (h)	kel (h)
Pharmaco (A)						
Mean	615.61	649.22	63.79386	1.298	23.360	0.03281
CV	35.1	35.7	41.1	39.3	31.7	34.4
Organon UK (B)						
Mean	597.61	632.02	58.12983	1.619	23.565	0.03247
CV	30.5	35.7	34.6	53.3	30.0	34.3
Organon Germany						
(C)	593.05	627.13	55.64525	1.660	23.205	0.03286
Mean	35.4	35.7	38.7	49.4	31.5	32.4
CV						

Table 2. Ratios of LSM% (90% Confidence Intervals) – Mirtazapine in Plasma

Parameter	Pharmaco (A) vs. Organon (Zispin®) (B)	Pharmaco (A) vs. Organon (Remergil® Soltab™)
AUC_{0-t}	103.1% (99.4% - 107.0%)	104.1% (100.3% - 108.0%)
AUC_{inf}	102.8% (99.1% - 106.7%)	103.8% (100.1% - 107.6%)
C_{max}	109.8% (102.2% - 118.0%	115.1% (107.1% - 123.7%)

The 90% confidence intervals derived from the analyses of the In-transformed PK parameters AUC_{0-t} and C for mirtazapine and N-demethylmirtazapine in plasma were within the 80% to 125% acceptance range for the Pharmaco (A) vs. Organon (Zispin®) (B) formulations and the Pharmaco (A) vs. Organon (Remergil® Soltab™) formulations.

Based on these results, the Pharmaco 30 mg orodispersible mirtazapine tablets are bioequivalent to the Organon Laboratories Limited (Zispin®) 30 mg mirtazapine tablets and the Organon Laboratories Limited (Remergil® Soltab™) 30 mg orodispersible mirtazapine tablets.

The essentially linear pharmacokinetics of mirtazapine makes it likely that the other doses of mirtazapine formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

Overall, 45 subjects (100% of the study population) experienced at least 1 adverse event that was possibly, probably, or definitely related to Treatment A; 38 subjects

(84.4% of the study population) experienced at least 1 adverse event that was possibly, probably, or definitely related to Treatment B; and 44 subjects (97.8% of the study population) experienced at least 1 adverse event that was possibly, probably, or definitely related to Treatment C.

There were no serious adverse events that occurred during the conduct of this study.

TOXICOLOGY
No new data are provided or required. However, the applicant has submitted a Preclinical Expert Report.

EFFICACY
No new data are provided. However, the applicant has provided a critical expert review of seventy-five publications which demonstrate the effectiveness and safety of mirtazapine.

SAFETY
No new data are submitted. The applicant has provided a review of the clinical safety of mirtazapine. Overall, the incidence of adverse effects compares favourably with that other related antidepressants such as amitriptyline. The most common adverse events of mirtazapine are sedation, weight gain and increased appetite.

EXPERT REPORT
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

CONCLUSIONS
The applicant has demonstrated bioequivalence. Marketing authorisations should be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Mirtazapine 15mg, 30mg and 45mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Based on the results the applicant's Mirtazapine 30 mg orodispersible tablets are bioequivalent to the Organon Laboratories Limited (Zispin®) 30 mg mirtazapine tablets and the Organon Laboratories Limited (Remergil® Soltab™) 30 mg orodispersible mirtazapine tablets.

Given that linear pharmacokinetics apply between the 30mg dose and the other doses (15mg and 45mg) of mirtazapine formulations, separate bioequivalence studies using the 15mg and 45mg tablets have not been considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with the active ingredient mirtazapine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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PL 08608/0114
PL 08608/0117

MIRTAZAPINE 30MG ORODISPERSIBLE TABLETS
PL 08608/0115
PL 08608/0118

MIRTAZAPINE 45MG ORODISPERSIBLE TABLETS
PL 08608/0116
PL 08608/0119

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 24th January 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 31st July 2005
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 31st July 2005, and further information relating to the quality dossiers on 17th February 2006, 4th December 2006 and 23rd March 2007.
4	The applicant responded to the MHRA's requests, providing further information on 24th October 2005 for the clinical section, and again on 27th August 2006, 15th March 2007 and 23rd March 2007 for the quality sections.
5	The applications were determined on 24th July 2007.

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MIRTAZAPINE 45MG ORODISPERSIBLE TABLETS
PL 08608/0116
PL 08608/0119

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
7th August 2007	PIQ-Label and Leaflet	Label and Leaflet-Self Certification- To correct typographical errors in the patient information leaflet (Only to PL 08608/0117-0119)	Approved

SUMMARY OF PRODUCT CHARACTERISTICS

PL 08608/0114 and PL 08608/0117

1 NAME OF THE MEDICINAL PRODUCT

Mirtazapine 15 mg orodispersible tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg of mirtazapine.
Excipient(s): 6 mg of Aspartame (E951)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orodispersible tablet
The tablets are white or almost white, 8 mm round, biconvex, uncoated tablets and marked M1.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of depressive illness.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The tablet should be taken out of the blister with dry hands and should be placed on the tongue.
The tablet will disintegrate and can be swallowed without water. The tablet should be swallowed without chewing.

Adults: Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45 mg.

Elderly: The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children: Since safety and efficacy of Mirtazapine has not been established in children, it is not recommended to treat children with Mirtazapine. Two randomised placebo-controlled trials failed to demonstrate efficacy for Mirtazapine in the treatment of children and adolescents with major depressive disorder. Safety and efficacy of Mirtazapine in paediatric depression can not be extrapolated from adult data.

The clearance of mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Mirtazapine to this category of patients.

Mirtazapine has a half-life of 20-40 hours and therefore Mirtazapine is suitable for going to bed. Mirtazapine may also be given in sub-doses equally divided over the day (once in the morning and once at night-time).

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

4.3 CONTRAINDICATIONS

Hypersensitivity to mirtazapine or any of the other ingredients of Mirtazapine orodispersible tablets.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Reversible white blood cell disorders including agranulocytosis, leukopenia and granulocytopenia have been reported as a rare occurrence with Mirtazapine. This mostly appears after 4-6 weeks of treatment and is in general reversible after termination of treatment With respect to agranulocytosis the physician should be alert to symptoms such as fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken. Patients should also be advised of the importance of these symptoms.

Careful dosing as well as regular and close monitoring is necessary in patients with:

- epilepsy and organic brain syndrome. As with other antidepressants, mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency. Antidepressants should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored. From clinical experience it appears that insults occur rarely in patients treated with Mirtazapine

- hepatic or renal insufficiency

- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered

- low blood pressure

- diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

As with other antidepressants care should be taken in patients with:

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because Mirtazapine possesses only very weak anticholinergic activity)

- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Mirtazapine because of its very weak anticholinergic activity)

Treatment should be discontinued if jaundice occurs.

Moreover, as with other antidepressants, the following should be taken into account:

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified

- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase

- as improvement may not occur during the first few weeks of treatment, in common with all antidepressants, patients should be closely monitored during this period. The possibility of suicide is inherent in depression, and may persist until significant remission occurs. It is general clinical experience with all therapies for depression, that the risk of suicide may increase in the early stages of recovery.

- although antidepressants are not addictive, the abrupt termination of treatment after long-term administration may result in nausea, headache and malaise

- elderly patients are often more sensitive, especially with regard to the side-effects of antidepressants. During clinical research with Mirtazapine, side-effects have not been reported more often in elderly patients than in other age groups; however, experience until now is limited.

Use in children and adolescents under 18 years of age
- Mirtazapine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

- Mirtazapine orodispersible tablets contain aspartame a source of phenylalanine. Each tablet with 15 mg mirtazapine corresponds to 3 mg phenylalanine, respectively. May be harmful for patients with phenylketonuria.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

- Mirtazapine may potentiate the central nervous dampening action of alcohol; patients should therefore be advised to avoid alcohol during treatment with Mirtazapine.

- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks of cessation of therapy with these agents.

- Mirtazapine may potentiate the sedative effects of benzodiazepines; caution should be taken when these drugs are prescribed together with Mirtazapine.

- In vitro data suggest that mirtazapine is a very weak competitive inhibitor of the cytochrome P450 enzymes CYP1A2, CYP2D6 and CYP3A.

- Caution is needed when strong CYP3A4 inhibitors, such as the HIV protease inhibitors, azole antifungals, erythromycin and nefazodone are co-administered with mirtazapine.

· Co-administration of the potent inhibitor of CYP3A4, ketoconazole increased the peak plasma levels and AUC by approximately 30 and 45% respectively.

· Carbamazepine, an inducer of CYP3A4, increased mirtazapine clearance about twofold, resulting in a decrease in plasma levels of 45-60%. Phenytoin increased the clearance of mirtazapine in a similar fashion. When carbamazepine or another inducer of drug metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with an inducer is stopped, mirtazapine dosing may have to be decreased.

· Bioavailability of mirtazapine increased by more than 50% when co-administered with cimetidine. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is ended.

· Mirtazapine caused a small but clinically insignificant increase in INR in subjects treated with warfarin.

Absence of interactions

· In *in vivo* interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline and cimetidine.

· No relevant clinical effects or changes in pharmacokinetics have been observed in man with concurrent administration of mirtazapine and lithium.

· A number of clinical interaction studies, and a study of mirtazapine treatment following SSRI treatment failure have been performed with mirtazapine and SSRIs. Until now no clinical interactions, pharmacodynamic or pharmacokinetic, have been encountered.

4.6 PREGNANCY AND LACTATION

The safety of Mirtazapine in human pregnancy has not been established.

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg (approx. 3 and 5 times respectively the maximum recommended human dose on the basis of exposure) have revealed no evidence of teratogenic effects. There was, however, in rats an increase in post-implantation loss; there was also an increase in pup deaths during the first three days of lactation (cause of death unknown) and a decrease in pup birth weights. These findings are common with CNS-active drugs at high dose levels in animals.

As the relevance of these findings to humans is not certain the use of Mirtazapine during pregnancy is not recommended. Women of child-bearing potential should employ an adequate method of contraception if taking Mirtazapine.

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of Mirtazapine in nursing mothers is not recommended since no human data in breast milk are available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

In some patients, particularly the elderly, Mirtazapine may have transient sedative properties and may initially impair alertness and concentration. Patients treated with

Mirtazapine should therefore be cautioned about their ability to drive a car or operate hazardous machinery

4.8 UNDESIRABLE EFFECTS

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Mirtazapine.
The following adverse effects have been reported:

	Rare >1/10,000)	Uncommon >1/1000)	Common >1/100)
Blood and the lymphatic system disorders	Reversible agranulocytosis has been reported as a rare occurrence with Mirtazapine. (see also section 4.4 'Special warnings and special precautions for use')		
Metabolism and nutrition disorders			Increase in appetite and weight gain
Psychiatric disorders	Nightmares/vivid dreams		
Nervous system disorders	Mania, convulsions (insults), tremor, myoclonus. There have been rare reports of agitation and hallucinations although these symptoms may be related to underlying disease. These effects have also been reported under placebo treatment in placebo-controlled studies with mirtazapine. Paraesthesia	Dizziness, Headache	
Cardiac disorders	(Orthostatic) hypotension.		
Hepato-biliary disorders		Increases in liver enzyme levels	
Skin and subcutaneous tissue disorders	Rash		
Musculoskeletal, connective tissue and	Restless legs, Arthralgia/myalgia		

bone disorders	
General disorders	Generalised or local oedema. Drowsiness/sedation/ fatigue, generally occurring during the first few weeks of treatment. (N.B. dose reduction generally does not lead to less sedation but can jeopardise antidepressant efficacy)

Although mirtazapine does not cause dependence, post-marketing experience shows that abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, nausea, anxiety and agitation are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realised that these symptoms may be related to underlying disease. As advised in section 4.2, treatment with mirtazapine should be discontinued gradually.

4.9 OVERDOSE

Present experience concerning overdose with Mirtazapine alone indicates that symptoms are usually mild.

Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

5 PHARMACOLOGICAL PROPERTIES

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. The presence of symptoms such as anhedonia, psychomotor inhibition, sleep disturbances (early wakening) and weight loss, increase the chance of a positive response. Other symptoms are: loss of interest, suicidal thoughts and changes in mood (better in the evening than in the morning). Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment.

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other Antidepressants, ATC code: NO6AX11

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

The histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration of Mirtazapine, the active constituent mirtazapine is rapidly and well absorbed (bioavailability 50%), reaching peak plasma levels after about 2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine. Mirtazapine is extensively metabolised and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites.The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. There are no differences in the pharmacokinetic parameters of racemic mirtazapine or its demethyl metabolite in extensive and poor metabolisers. Plasma metabolite profiles for the individual enantiomers are qualitatively similar in extensive and poor metabolisers.

The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3 PRECLINICAL SAFETY DATA

No special particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol DC
Microcrystalline cellulose
Crospovidone
Hydroxylpropyl cellulose low substituted
Magnesium carbonate heavy
Silica colloidal anhydrous
Methionine
Magnesium stearate
Guar Gum
Aspartame (E951)
Orange flavour

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

1. Al/Al Blister, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
2. Al/Al Blister with peel off foil, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
3. PP securitainers, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
4. HDPE containers with LDPE caps, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.

Not all pack sizes or types may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special precautions

7 MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited
38/40 Chamberlayne Road,
London, NW10 3JN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL08608/0114
PL08608/0117

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/07/2007

10 DATE OF REVISION OF THE TEXT

24/07/2007

PL 08608/0115 and PL 08608/0118

1 NAME OF THE MEDICINAL PRODUCT

Mirtazapine 30 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg of mirtazapine.
Excipient(s): 12 mg of Aspartame (E951)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orodispersible tablet
The tablets are white or almost white, 10 mm round, biconvex, uncoated tablets and marked M2.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of depressive illness.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The tablet should be taken out of the blister with dry hands and should be placed on the tongue.
The tablet will disintegrate and can be swallowed without water. The tablet should be swallowed without chewing.

Adults: Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45 mg.

Elderly: The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children: Since safety and efficacy of Mirtazapine has not been established in children, it is not recommended to treat children with Mirtazapine. Two randomised placebo-controlled trials failed to demonstrate efficacy for Mirtazapine in the treatment of children and adolescents with major depressive disorder. Safety and efficacy of Mirtazapine in paediatric depression can not be extrapolated from adult data.

The clearance of mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Mirtazapine to this category of patients.

Mirtazapine has a half-life of 20-40 hours and therefore Mirtazapine is suitable for once-a-day administration. It should be taken preferably as a single night-time dose before going to bed. Mirtazapine may also be given in sub-doses equally divided over the day (once in the morning and once at night-time).

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

4.3 CONTRAINDICATIONS

Hypersensitivity to mirtazapine or any of the other ingredients of Mirtazapine orodispersible tablets.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Reversible white blood cell disorders including agranulocytosis, leukopenia and granulocytopenia have been reported as a rare occurrence with Mirtazapine. This mostly appears after 4-6 weeks of treatment and is in general reversible after termination of treatment With respect to agranulocytosis the physician should be alert to symptoms such as fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken. Patients should also be advised of the importance of these symptoms.

Careful dosing as well as regular and close monitoring is necessary in patients with:

- epilepsy and organic brain syndrome. As with other antidepressants, mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency. Antidepressants should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored. From clinical experience it appears that insults occur rarely in patients treated with Mirtazapine

- hepatic or renal insufficiency

- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered

- low blood pressure

- diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

As with other antidepressants care should be taken in patients with:

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because Mirtazapine possesses only very weak anticholinergic activity)

- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Mirtazapine because of its very weak anticholinergic activity)

Treatment should be discontinued if jaundice occurs.

Moreover, as with other antidepressants, the following should be taken into account:

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified

- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase

- as improvement may not occur during the first few weeks of treatment, in common with all antidepressants, patients should be closely monitored during this period. The possibility of suicide is inherent in depression, and may persist until significant remission occurs. It is general clinical experience with all therapies for depression, that the risk of suicide may increase in the early stages of recovery.

- although antidepressants are not addictive, the abrupt termination of treatment after long-term administration may result in nausea, headache and malaise

- elderly patients are often more sensitive, especially with regard to the side-effects of antidepressants. During clinical research with Mirtazapine, side-effects have not been reported more often in elderly patients than in other age groups; however, experience until now is limited.

- Use in children and adolescents under 18 years of age. Mirtazapine Orodispersible Tablets should not be used in the treatment of children and adolescents under the age of 18 years.. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

- Mirtazapine orodispersible tablets contain aspartame a source of phenylalanine. Each tablet with 30 mg mirtazapine corresponds to 6 mg phenylalanine, respectively. May be harmful for patients with phenylketonuria.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

- Mirtazapine may potentiate the central nervous dampening action of alcohol; patients should therefore be advised to avoid alcohol during treatment with Mirtazapine.

- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks of cessation of therapy with these agents.

- Mirtazapine may potentiate the sedative effects of benzodiazepines; caution should be taken when these drugs are prescribed together with Mirtazapine.

- In vitro data suggest that mirtazapine is a very weak competitive inhibitor of the cytochrome P450 enzymes CYP1A2, CYP2D6 and CYP3A.

- Caution is needed when strong CYP3A4 inhibitors, such as the HIV protease inhibitors, azole antifungals, erythromycin and nefazodone are co-administered with mirtazapine.

· Co-administration of the potent inhibitor of CYP3A4, ketoconazole increased the peak plasma levels and AUC by approximately 30 and 45% respectively.

· Carbamazepine, an inducer of CYP3A4, increased mirtazapine clearance about twofold, resulting in a decrease in plasma levels of 45-60%. Phenytoin increased the clearance of mirtazapine in a similar fashion. When carbamazepine or another inducer of drug metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with an inducer is stopped, mirtazapine dosing may have to be decreased.

· Bioavailability of mirtazapine increased by more than 50% when co-administered with cimetidine. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is ended.

· Mirtazapine caused a small but clinically insignificant increase in INR in subjects treated with warfarin.

Absence of interactions

· In *in vivo* interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline and cimetidine.

· No relevant clinical effects or changes in pharmacokinetics have been observed in man with concurrent administration of mirtazapine and lithium.

· A number of clinical interaction studies, and a study of mirtazapine treatment following SSRI treatment failure have been performed with mirtazapine and SSRIs. Until now no clinical interactions, pharmacodynamic or pharmacokinetic, have been encountered.

4.6 PREGNANCY AND LACTATION

The safety of Mirtazapine in human pregnancy has not been established.

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg (approx. 3 and 5 times respectively the maximum recommended human dose on the basis of exposure) have revealed no evidence of teratogenic effects. There was, however, in rats an increase in post-implantation loss; there was also an increase in pup deaths during the first three days of lactation (cause of death unknown) and a decrease in pup birth weights. These findings are common with CNS-active drugs at high dose levels in animals.

As the relevance of these findings to humans is not certain the use of Mirtazapine during pregnancy is not recommended. Women of child-bearing potential should employ an adequate method of contraception if taking Mirtazapine.

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of Mirtazapine in nursing mothers is not recommended since no human data in breast milk are available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

In some patients, particularly the elderly, Mirtazapine may have transient sedative properties and may initially impair alertness and concentration. Patients treated with Mirtazapine should therefore be cautioned about their ability to drive a car or operate hazardous machinery

4.8 UNDESIRABLE EFFECTS

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Mirtazapine.
The following adverse effects have been reported:

	Rare >1/10,000)	Uncommon >1/1000)	Common >1/100)
Blood and the lymphatic system disorders	Reversible agranulocytosis has been reported as a rare occurrence with Mirtazapine. (see also section 4.4 'Special warnings and special precautions for use')		
Metabolism and nutrition disorders			Increase in appetite and weight gain
Psychiatric disorders	Nightmares/vivid dreams		
Nervous system disorders	Mania, convulsions (insults), tremor, myoclonus. There have been rare reports of agitation and hallucinations although these symptoms may be related to underlying disease. These effects have also been reported under placebo treatment in placebo-controlled studies with mirtazapine. Paraesthesia	Dizziness, Headache	
Cardiac disorders	(Orthostatic) hypotension.		
Hepato-biliary disorders		Increases in liver enzyme levels	
Skin and subcutaneous tissue disorders	Rash		

Musculoskeletal, connective tissue and bone disorders	Restless legs, Arthralgia/myalgia	
General disorders		Generalised or local oedema. Drowsiness/sedation/ fatigue, generally occurring during the first few weeks of treatment. (N.B. dose reduction generally does not lead to less sedation but can jeopardise antidepressant efficacy)

Although mirtazapine does not cause dependence, post-marketing experience shows that abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, nausea, anxiety and agitation are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realised that these symptoms may be related to underlying disease. As advised in section 4.2, treatment with mirtazapine should be discontinued gradually.

4.9 OVERDOSE

Present experience concerning overdose with Mirtazapine alone indicates that symptoms are usually mild.

Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

5 PHARMACOLOGICAL PROPERTIES

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. The presence of symptoms such as anhedonia, psychomotor inhibition, sleep disturbances (early wakening) and weight loss, increase the chance of a positive response. Other symptoms are: loss of interest, suicidal thoughts and changes in mood (better in the evening than in the morning). Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment.

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other Antidepressants, ATC code: NO6AX11

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

The histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration of Mirtazapine, the active constituent mirtazapine is rapidly and well absorbed (bioavailability 50%), reaching peak plasma levels after about 2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine. Mirtazapine is extensively metabolised and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites.The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. There are no differences in the pharmacokinetic parameters of racemic mirtazapine or its demethyl metabolite in extensive and poor metabolisers. Plasma metabolite profiles for the individual enantiomers are qualitatively similar in extensive and poor metabolisers.

The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3 PRECLINICAL SAFETY DATA

No special particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol DC
Microcrystalline cellulose
Crospovidone
Hydroxylpropyl cellulose low substituted
Magnesium carbonate heavy
Silica colloidal anhydrous
Methionine
Purified water
Magnesium stearate
Guar Gum
Aspartame (E951)
Orange flavour

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
1. Al/Al Blister, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
2. Al/Al Blister with peel off foil, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
3 . PP securitainers, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
4. HDPE containers with LDPE caps, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special precautions

7 MARKETING AUTHORISATION HOLDER
Olinka (UK) Limited
38/40 Chamberlayne Road,
London, NW10 3JN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL08608/0115
PL08608/0118

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/07/2007

10 DATE OF REVISION OF THE TEXT
24/07/2007

PL 08608/0116 and PL 08608/0119

1 NAME OF THE MEDICINAL PRODUCT

Mirtazapine 45 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 45 mg of mirtazapine.
Excipient(s): 18 mg of Aspartame (E951)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orodispersible tablet
The tablets are white or almost white, 12 mm round, biconvex, uncoated tablets and marked M4.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of depressive illness.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The tablet should be taken out of the blister with dry hands and should be placed on the tongue.
The tablet will disintegrate and can be swallowed without water. The tablet should be swallowed without chewing.

Adults: Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45 mg.

Elderly: The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children: Since safety and efficacy of Mirtazapine has not been established in children, it is not recommended to treat children with Mirtazapine. Two randomised placebo-controlled trials failed to demonstrate efficacy for Mirtazapine in the treatment of children and adolescents with major depressive disorder. Safety and efficacy of Mirtazapine in paediatric depression can not be extrapolated from adult data.

The clearance of mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Mirtazapine to this category of patients.

Mirtazapine has a half-life of 20-40 hours and therefore Mirtazapine is suitable for once-a-day administration. It should be taken preferably as a single night-time dose before going to bed. Mirtazapine may also be given in sub-doses equally divided over the day (once in the morning and once at night-time).

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

4.3 CONTRAINDICATIONS

Hypersensitivity to mirtazapine or any of the other ingredients of Mirtazapine orodispersible tablets.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Reversible white blood cell disorders including agranulocytosis, leukopenia and granulocytopenia have been reported as a rare occurrence with Mirtazapine. This mostly appears after 4-6 weeks of treatment and is in general reversible after termination of treatment With respect to agranulocytosis the physician should be alert to symptoms such as fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken. Patients should also be advised of the importance of these symptoms.

Careful dosing as well as regular and close monitoring is necessary in patients with:

- epilepsy and organic brain syndrome. As with other antidepressants, mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency. Antidepressants should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored. From clinical experience it appears that insults occur rarely in patients treated with Mirtazapine

- hepatic or renal insufficiency

- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered

- low blood pressure

- diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

As with other antidepressants care should be taken in patients with:

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because Mirtazapine possesses only very weak anticholinergic activity)

- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Mirtazapine because of its very weak anticholinergic activity)

Treatment should be discontinued if jaundice occurs.

Moreover, as with other antidepressants, the following should be taken into account:

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified

- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase

- as improvement may not occur during the first few weeks of treatment, in common with all antidepressants, patients should be closely monitored during this period. The possibility of suicide is inherent in depression, and may persist until significant remission occurs. It is general clinical experience with all therapies for depression, that the risk of suicide may increase in the early stages of recovery.

- although antidepressants are not addictive, the abrupt termination of treatment after long-term administration may result in nausea, headache and malaise

- elderly patients are often more sensitive, especially with regard to the side-effects of antidepressants. During clinical research with Mirtazapine, side-effects have not been reported more often in elderly patients than in other age groups; however, experience until now is limited.

- Use in children and adolescents under 18 years of age. Mirtazapine Orodispersible Tablets should not be used in the treatment of children and adolescents under the age of 18 years.. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

- Mirtazapine orodispersible tablets contain aspartame a source of phenylalanine. Each tablet with 45 mg mirtazapine corresponds to 9 mg phenylalanine, respectively. May be harmful for patients with phenylketonuria.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

- Mirtazapine may potentiate the central nervous dampening action of alcohol; patients should therefore be advised to avoid alcohol during treatment with Mirtazapine.

- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks of cessation of therapy with these agents.

- Mirtazapine may potentiate the sedative effects of benzodiazepines; caution should be taken when these drugs are prescribed together with Mirtazapine.

- In vitro data suggest that mirtazapine is a very weak competitive inhibitor of the cytochrome P450 enzymes CYP1A2, CYP2D6 and CYP3A.

- Caution is needed when strong CYP3A4 inhibitors, such as the HIV protease inhibitors, azole antifungals, erythromycin and nefazodone are co-administered with mirtazapine.

· Co-administration of the potent inhibitor of CYP3A4, ketoconazole increased the peak plasma levels and AUC by approximately 30 and 45% respectively.

· Carbamazepine, an inducer of CYP3A4, increased mirtazapine clearance about twofold, resulting in a decrease in plasma levels of 45-60%. Phenytoin increased the clearance of mirtazapine in a similar fashion. When carbamazepine or another inducer of drug metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with an inducer is stopped, mirtazapine dosing may have to be decreased.

· Bioavailability of mirtazapine increased by more than 50% when co-administered with cimetidine. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is ended.

· Mirtazapine caused a small but clinically insignificant increase in INR in subjects treated with warfarin.

Absence of interactions

· In *in vivo* interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline and cimetidine.

· No relevant clinical effects or changes in pharmacokinetics have been observed in man with concurrent administration of mirtazapine and lithium.

· A number of clinical interaction studies, and a study of mirtazapine treatment following SSRI treatment failure have been performed with mirtazapine and SSRIs. Until now no clinical interactions, pharmacodynamic or pharmacokinetic, have been encountered.

4.6 PREGNANCY AND LACTATION

The safety of Mirtazapine in human pregnancy has not been established.

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg (approx. 3 and 5 times respectively the maximum recommended human dose on the basis of exposure) have revealed no evidence of teratogenic effects. There was, however, in rats an increase in post-implantation loss; there was also an increase in pup deaths during the first three days of lactation (cause of death unknown) and a decrease in pup birth weights. These findings are common with CNS-active drugs at high dose levels in animals.

As the relevance of these findings to humans is not certain the use of Mirtazapine during pregnancy is not recommended. Women of child-bearing potential should employ an adequate method of contraception if taking Mirtazapine.

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of Mirtazapine in nursing mothers is not recommended since no human data in breast milk are available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

In some patients, particularly the elderly, Mirtazapine may have transient sedative properties and may initially impair alertness and concentration. Patients treated with

Mirtazapine should therefore be cautioned about their ability to drive a car or operate hazardous machinery

4.8 UNDESIRABLE EFFECTS

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Mirtazapine.
The following adverse effects have been reported:

	Rare >1/10,000)	Uncommon >1/1000)	Common >1/100)
Blood and the lymphatic system disorders	Reversible agranulocytosis has been reported as a rare occurrence with Mirtazapine. (see also section 4.4 'Special warnings and special precautions for use')		
Metabolism and nutrition disorders			Increase in appetite and weight gain
Psychiatric disorders	Nightmares/vivid dreams		
Nervous system disorders	Mania, convulsions (insults), tremor, myoclonus. There have been rare reports of agitation and hallucinations although these symptoms may be related to underlying disease. These effects have also been reported under placebo treatment in placebo-controlled studies with mirtazapine. Paraesthesia	Dizziness, Headache	
Cardiac disorders	(Orthostatic) hypotension.		
Hepato-biliary disorders		Increases in liver enzyme levels	
Skin and subcutaneous tissue disorders	Rash		
Musculoskeletal, connective tissue and	Restless legs, Arthralgia/myalgia		

bone disorders	
General disorders	Generalised or local oedema. Drowsiness/sedation/ fatigue, generally occurring during the first few weeks of treatment. (N.B. dose reduction generally does not lead to less sedation but can jeopardise antidepressant efficacy)

Although mirtazapine does not cause dependence, post-marketing experience shows that abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, nausea, anxiety and agitation are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realised that these symptoms may be related to underlying disease. As advised in section 4.2, treatment with mirtazapine should be discontinued gradually.

4.9 OVERDOSE

Present experience concerning overdose with Mirtazapine alone indicates that symptoms are usually mild.

Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

5 PHARMACOLOGICAL PROPERTIES

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. The presence of symptoms such as anhedonia, psychomotor inhibition, sleep disturbances (early wakening) and weight loss, increase the chance of a positive response. Other symptoms are: loss of interest, suicidal thoughts and changes in mood (better in the evening than in the morning). Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment.

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other Antidepressants, ATC code: NO6AX11

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

The histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no

anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration of Mirtazapine, the active constituent mirtazapine is rapidly and well absorbed (bioavailability 50%), reaching peak plasma levels after about 2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine. Mirtazapine is extensively metabolised and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites.The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. There are no differences in the pharmacokinetic parameters of racemic mirtazapine or its demethyl metabolite in extensive and poor metabolisers. Plasma metabolite profiles for the individual enantiomers are qualitatively similar in extensive and poor metabolisers.

The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3 PRECLINICAL SAFETY DATA

No special particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol DC
Microcrystalline cellulose
Crospovidone
Hydroxylpropyl cellulose low substituted
Magnesium carbonate heavy
Silica colloidal anhydrous
Methionine
Purified water
Magnesium stearate
Guar Gum Aspartame (E951)
Orange flavour

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

1. Al/Al Blister, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
2. Al/Al Blister with peel off foil, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
3 . PP securitainers, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.
4 . HDPE containers with LDPE caps, pack sizes; 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special precautions

7 MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited
38/40 Chamberlayne Road,
London, NW10 3JN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL08608/0116
PL08608/0119

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/07/2007

10 DATE OF REVISION OF THE TEXT

24/07/2007

PATIENT INFORMATION LEAFLET

O·L·I·N·K·A

PACKAGE LEAFLET: INFORMATION FOR THE USER

Mirtazapine 15mg, 30mg and 45mg Orodispersible Tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours

In this leaflet:

1. WHAT MIRTAZAPINE ORODISPERSIBLE TABLETS ARE AND WHAT THEY ARE USED FOR

Mirtazapine belongs to a group of medicines called antidepressants and is used to treat depression.

It may take 2 to 4 weeks before you start to feel or sleep better. It is important to take Mirtazapine every day and not to stop taking it unless your doctor tells you to. If you do, your symptoms may come back.

2. BEFORE YOU TAKE MIRTAZAPINE ORODISPERSIBLE TABLETS

Do not take Mirtazapine

If you are **allergic** (hypersensitive) to mirtazapine or any of the other ingredients of Mirtazapine Orodispersible tablets (see section 6).

Take special care with Mirtazapine if you have or have had:
- epilepsy (seizures or fits)
- kidney or liver disease (including jaundice)
- heart disease
- low blood pressure
- difficulty in passing water (urinating), which may be caused by an enlarged prostate
- eye disease, such as glaucoma
- diabetes
- psychiatric disorders such as schizophrenia or manic depression

In rare cases there may be changes in the white blood cells.
If you get fever, sore mouth or throat and recurrent minor infections such as coughs and colds tell your doctor as you may need to stop taking your medicine.

Children and adolescents under 18 years of age

Mirtazapine should normally not be used for children and adolescents under 18 years except for patients with depression. Patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (mainly aggression, oppositional behaviour and anger) when they take this type of medicines. Despite this, your doctor may prescribe Mirtazapine for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Mirtazapine for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Mirtazapine. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development in this age group have not yet been demonstrated

Taking other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
- Other antidepressants:

You should not take Mirtazapine Orodipsersible tablets if you are taking other antidepressants known as Monoamine Oxidase Inhibitors (MAOIs), or in the two weeks after they have been stopped. The use of other antidepressants or medicines containing the product serotonin can lead to the development of serotonin syndrome and should be used with caution.
- Drugs for anxiety or insomnia:

Mirtazapine can increase the drowsiness caused by benzodiazepines.
- Take care when taking any of the following medicines:
  - drugs used in the treatment of HIV
  - antibiotics such as erythromycin or rifampicin
  - antifungal agents such as ketoconazole
  - nefazodone, an antidepressant
  - drugs for epilepsy e.g. phenytoin or carbamazapine
  - cimetidine a drug used to treat for indigestion or stomach ulcers
  - drugs to prevent blood clotting e.g. warfarin

Taking Mirtazapine with food and drink

You may get drowsy if you drink alcohol while you are taking Mirtazapine. It is therefore advisable to avoid drinking any alcohol.

Pregnancy and breastfeeding

Ask your doctor or pharmacist for advice before taking this medicine, as mirtazapine should not be taken if you are pregnant, trying to become pregnant or are breastfeeding.

Driving and using machines

Mirtazapine can make you drowsy, affect your concentration or make you less alert. When you first start taking Mirtazapine, make sure your abilities are not affected before you drive or operate machinery.

Important information about some of the ingredients of Mirtazapine

Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

3. HOW TO TAKE MIRTAZAPINE ORODISPERSIBLE TABLETS

Important: only take Mirtazapine as your doctor or pharmacist tells you to. Don't stop taking it unless your doctor tells you to.

Adults and elderly patients:

The usual starting dose is 15mg, taken preferably in the evening. Your doctor may advise you to increase your dose after a few days to the amount that may be best for you.

Patients with kidney or liver problems may be given a lower dose of Mirtazapine.

Duration of Treatment:

After 2 to 4 weeks, talk to your doctor about the effect the treatment has had. If you still don't feel well, your doctor may prescribe a higher dose. After another 2 to 4 weeks talk to your doctor again.

If you have the impression that the effect of Mirtazapine is too strong or too weak, talk to your doctor or pharmacist.

Method and Route of Administration:

Your doctor will probably advise you to take Mirtazapine as a single dose before you go to bed, as it may help you to sleep. However,

your doctor may suggest you split your dose - for example one tablet in the morning, and another in the evening before you go to bed.

Take the tablets as follows;

Fig A
Keep your hands dry.
Do not push the tablet out of the pocket (Fig A).
You will crush it.

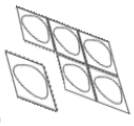

Fig B
Each strip contains six tablets.
The tablets are in pockets separated by perforations.
Tear off one tablet pocket along the dotted line (Fig B)

Fig C
Carefully peel off the foil starting at the corner with the black arrow. (Fig C and D)

Fig D

Fig E
Put the tablet on your tongue. The tablet will disintegrate and can be swallowed without water.

If you take more Mirtazapine than you should
Call a doctor straight away or go immediately to the nearest casualty department, taking the remaining tablets with you. The most likely signs of overdose are drowsiness and disorientation.

If you forget to take Mirtazapine
Do not take a double dose to make up for forgotten individual doses. Just skip that dose and take your next one at the normal time.

Effects when treatment with Mirtazapine is stopped
Do not suddenly stop taking Mirtazapine even if your depression has lifted. If you stop suddenly, you may feel sick, anxious or agitated and have headaches. It is possible that some of your symptoms may come back.
Once you are feeling better, talk to your doctor who will tell you how to reduce the dose gradually. This will usually be about 4 to 6 months after you start feeling better.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Mirtazapine can have side effects. Please remember that it can sometimes be hard to tell the difference between some of the milder side effects and the symptoms of your depression.

If you experience any of the following events you should tell your doctor immediately:
Uncommon (occurs in1 to 10 in 1,000 users)
- Increased liver enzyme levels (seen in blood tests)

Rare (occurs in 1 to 10 in 10,000 users)
- Fits (seizures or convulsions)
- An allergic reaction; signs are swelling of the lips, face and tongue, difficulty breathing, feeling faint
- Signs of infection such as fever, sore throat, mouth ulcer or stomach upset. In very rare cases, people become less resistant to infection in the first few weeks of taking Mirtazapine, as it can cause a temporary shortage of white blood cells. If you have these symptoms, your doctor will arrange a blood test to check.

Other side effects
The following events are less serious but you may wish to discuss them with your doctor or pharmacist if they become troublesome or last a long time:
Common (occurs in 1 in 100 users)
- Increase in appetite and weight gain
- Drowsiness during the first few weeks of treatment
- Swollen ankles caused by fluid retention (oedema)

Uncommon (occurs in 1 to 10 in 1,000 users)
- Dizziness
- Headaches

Rare (occurs in 1 to 10,000 users)
- Mania (feeling elated or emotionally 'high')
- Nightmares, wild dreams or hallucinations
- Feeling agitated
- A rash or skin eruptions
- Shakiness or tremor
- Muscle twitching or contractions or 'restless legs'
- Pains in your joints or muscles
- Numbness or 'pins and needles' (paraesthesia)
- Feeling dizzy or faint especially when you stand up quickly

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING MIRTAZAPINE ORODISPERSIBLE TABLETS

Keep out of the reach and sight of children
Do not store above 25°C. Store in the original package in order to protect from light.
Do not use after the expiry date stated on the carton or foil.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Mirtazapine Orodispersible tablets contain
- The active substance is mirtazapine. Each tablet contains either 15mg, 30mg and 45mg of the active ingredient mirtazapine.
- The other ingredients are mannitol DC, microcrystalline cellulose, crospovidone, hydroxylpropyl cellulose low substituted, magnesium carbonate heavy, silica colloidal anhydrous, methionine, magnesium stearate, guar gum, aspartame (E951), orange flavour.

Each Mirtazapine orodispersible tablets is a white, round, biconvex, uncoated tablet with the following markings:
15mg orodispersible tablets - M1
30mg orodispersible tablets - M2.
45mg orodispersible tablets - M4.
The tablets are supplied in blister packs of 5, 6, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98 and 100 Tablets.**
** *(Final printed leaflet to include only marketed pack sizes).*

Marketing Authorisation holder and manufacturers
Marketing Authorisation Holder:
Olinka (UK) Limited, 38/40 Chamberlayne Road, London, NW10 3JN, United Kingdom
Manufactured by:
Actavis Limited, B16, Bulebel Industrial Estate, Zejtun ZTN 08 Malta***
Actavis hf Reykjavikurvegi 78, P.O.Box 420, IS-222 Harfnarfjordur Iceland***
****(Final printed leaflet to include the only release site for product)*
This leaflet was last revised in November 2006

LABELLING

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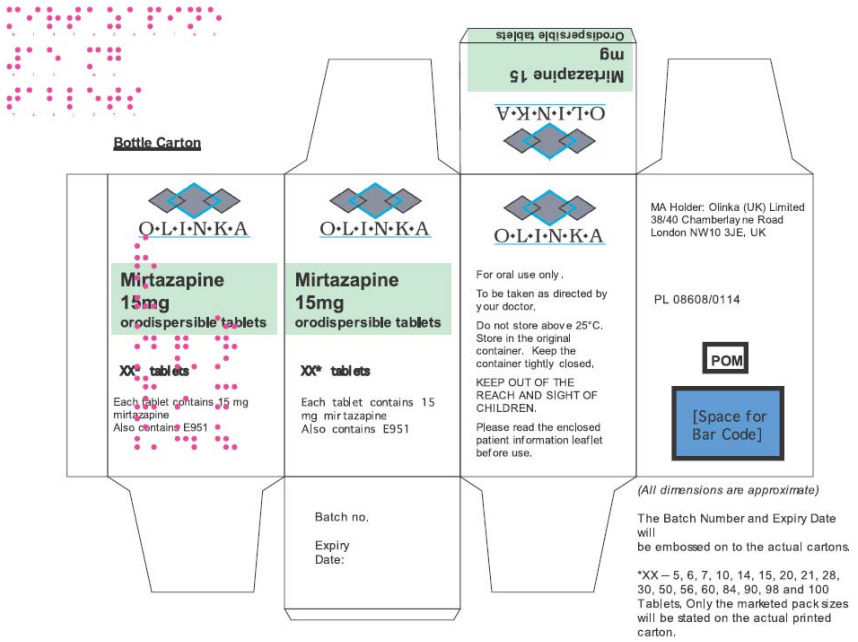

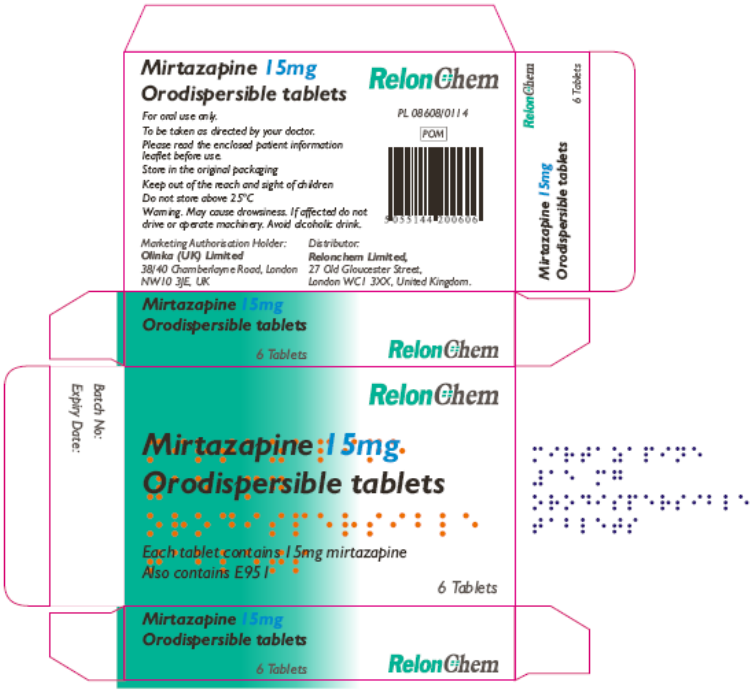

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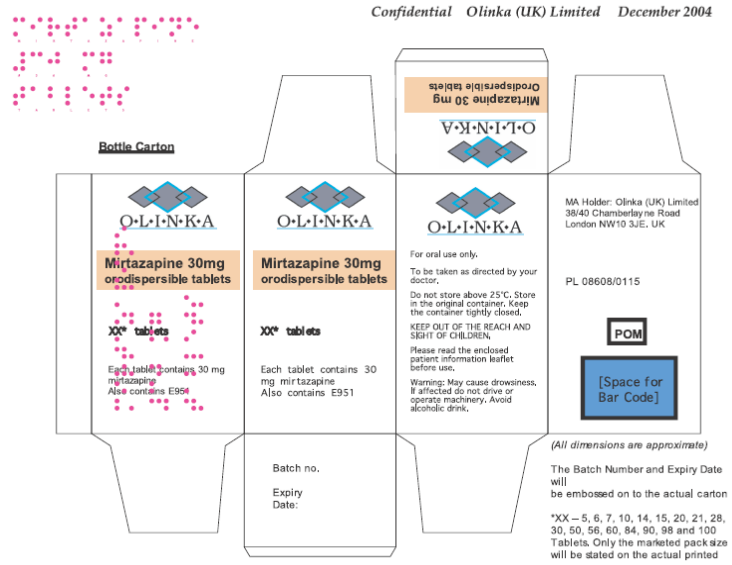

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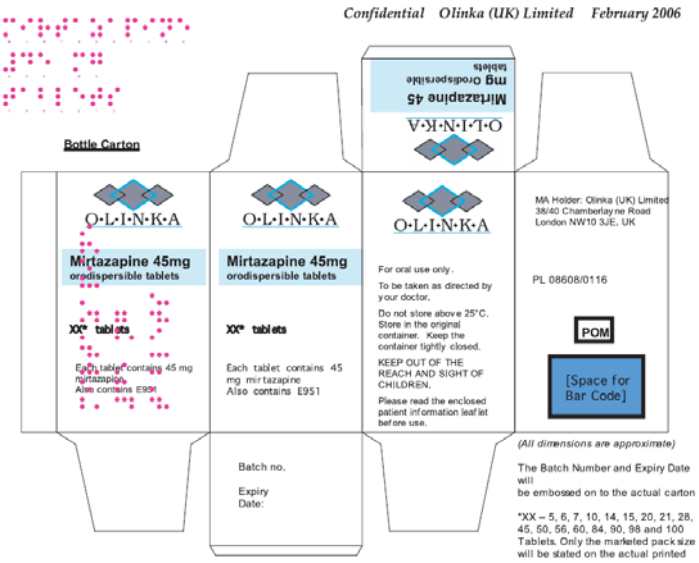

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